THE YALE JOURNAL OF BIOLOGY AND MEDICINE 55 (1982), 239-246

The Triple Helix—NIH, Industry, and the Academic World

CHARLES U. LOWE, M.D.

Associate Director for Medical Applications of Research (Acting), National Institutes of Health, Bethesda, Maryland

Received June 1, 1982

Spectacular accomplishments in biomedical research have given birth to what is now perceived as a biological revolution, an epoch in which man has acquired the skill to manipulate the fundamental unit of heredity, the gene.

This revolution carries with it the prospect of remarkable opportunities to improve the quality of life and to probe with increasing precision the mysteries of cellular organization and function. It comes, however, at a time when the opportunity to exploit this new knowledge may be limited by a significant reduction in federal support of basic research, and a situation which prompts universities and other centers of scientific activity to seek funding from industrial patrons. This trend has generated a new constellation of institutional challenges, for one apparent result of industrial sponsorship of university-based biomedical research is a threat to university governance as altered allegiances emerge and as the potential for financial gain appears almost limitless. This essay explores background issues leading to these new alliances, seeks to identify some of the central problems emerging for university administrators, faculty, and students, and then poses a key question: Can industrial support for university-based biomedical research fill the apparent short-fall in federal dollars in the foreseeable future? An analysis of available data indicates that this outcome is unlikely either now or in the years ahead.

American biomedical research organizes around a triangle of interests formed by industry, universities, and government. These same institutions provide the laboratories for virtually all of this research activity; the federal government serves as the primary patron. The federal role in developing and sustaining the nation's biomedical research capacity is almost universally acknowledged, and the success of the NIH is a monument to this commitment. Even in this day of budgetary constraints, the federal responsibility has been reaffirmed by both the administration and the Congress.

I have chosen to call this biomedical research complex a triple helix, borrowing from the language of cell biology. The analogy seems serviceable for it suggests that the triple helix, like the double helix, has both structural and functional attributes. Just as intracellular feedback modulates DNA function, so the need to balance the intellectual independence of the scientist with the industrial appetite for commercial opportunity tempers the partners in the triple helix. Within this structure the federal partner is held accountable to assure that the public dollar is spent in the public interest both directly and indirectly.

Presented in part at a Symposium "Academic-Industry Interactions," sponsored by the American Society of Biological Chemists; Meeting of the Federation of American Societies for Experimental Biology, New Orleans, Louisiana, April 18, 1982

Address reprint requests to: Charles U. Lowe, M.D., National Institutes of Health, Building 1, Room 238, Bethesda, MD 20205

The tensions within the academic world which justify this timely review of industry-university relations emerge from a concatenation of events. The capstone of achievement which led to the biological revolution so dazzled the scientific world that comparatively little attention has been given to the other notable incidents that have influenced its immediate effect. It is these modifying events that deserve our attention, for they appear to be central to the assessment of the new patterns of industry-university relations.

1. The most critical event was the scientific achievement of gene splicing—the ability to insert genetic instruction into a cell and thus endow it with the capability of producing a predetermined gene product.
2. This achievement was soon followed by the Supreme Court sanction for patenting manmade cellular configurations, in effect establishing in law that fabricated genes have a commercial value.
3. Following this, a patent court instructed the U.S. Patent Office to issue patents for products of this nature.
4. Simultaneously, the Congress modified patent statutes by conveying to universities the ownership of patents developed with federal support by their faculties.
5. At the same time there occurred a sharpening of competition for the ever more slowly growing federal research dollar, and other research funds seemed in short supply.
6. And once again scientists in profit-making organizations had equal standing with university scientists in seeking NIH grants, a situation which had not existed since 1968.
7. The political climate in which this drama unfolded was favorable to commercializing new technologies, particularly those developed with federal funding.
8. Finally, the universities held the key patents for recombinant DNA technology and supported a large pool of knowledgeable scientists, strategically placed to exploit this technology.

If these events had occurred at different times, history would have found each noteworthy. The fact that all occurred within a remarkably short period of time created a scientific epoch. They appear to have taken most of the major players by surprise. It is astonishing that risk capital to develop the new technology appeared so quickly. Investors had limited experience in judging the commercial value of biotechnical innovation, and for the most part knew neither the prospective market nor the nature of the products.

Before the eyes of faculty as well as university corporations appeared a vertiginous vision of riches beyond the dreams of avarice. This apparition became reality and grew spectacularly from a glimmer in the eye of some imaginative scientists to a whole new industry comprising 400 corporations and partnerships. Capitalization is estimated at 1 billion dollars and projected profits over the next decade may reach 40 billion dollars.

The U.S. Patent Office needed a new type of personnel, examiners capable of contending with the biomedical jargon found in applications to patent modified living organisms. Universities also were caught unaware, for most had no patent office, let alone a patent policy. Of the 1,200 institutions to which NIH awards grants or contracts only 82 had an Institutional Patent Agreement with NIH.

Many industrialists were equally unprepared. Some imaginative executives quickly realized the commercial possibilities of what had been a scientific activity conducted principally in university laboratories. They proceeded to seek information from knowledgeable scientists, patents and licenses from universities, and access to university laboratories. And when opportunities for joint ventures with university scientists were infeasible, at least 40 major corporations took equity positions in the most attractive of the new high technology ventures to establish a financial position in this rapidly expanding field.

The frenetic action appears to be abating, though the ferment continues. Scientists are weighing whether to remain in the academic world or accept entrepreneurial opportunities. Concomitantly, government and the Congress are examining the nation's position in biotechnology, to guage the impact on trade balances, as well as on the growth of the gross national product.

The biological revolution has occurred within the context of established institutional arrangements for conducting biomedical research and against a background of an historically productive, albeit modest, interaction between industry and universities. Why then is there a sudden, even dramatic and widespread interest in reviewing existing arrangements? The simplest explanation is that in the past the relations generally offered limited economic benefit for the university and the faculty. This is no longer the case, and, in addition, the level of federal and private nonprofit support for biomedical research is constrained.

Traditional university-industry interactions were limited largely to departments of physical sciences, engineering, and chemistry, and consequently university bylaws on consultation were generally designed to encompass low-key, but nonetheless important activities in non-biomedical fields. Just as the universities were unprepared for the stresses generated by the biological revolution, so biomedical scientists may have lacked the extensive and sophisticated experience of scientists in these other disciplines.

The effect was to place unrestrained temptation before the scientist and the university—a temptation neither was fully prepared to deal with realistically or rationally. If some abuses did take place, they forced universities to take stock, not only to avoid problems in the future but also out of concern for their own image.

What differentiates the effect of recombinant DNA technology from the impact of any other major scientific success? An examination of another technology which came to fruition in the recent past is informative. The silicon-chip technology, in its early stages, presented many similarities to the contemporary picture of biotechnology: a scientific revolution; a huge influx of venture capital; the creation of many small, high technology companies; opportunity for these companies to accumulate great wealth; and university faculty involvement as consultants and even equity partners with the new industrialists. Despite these similarities, silicon technology produced few of the destabilizing effects of the biological revolution. What is the distinction between these scientific epochs? First, the prevailing patent statutes gave few universities the chance to realize large sums of money from silicon-chip technology. A second difference follows from the nature of biomedical science: the investigators' apparent conservative attitude toward inventions and an increased sense of professional responsibility.

Biomedical science was built upon and continues to interact with the health care system and tends to recruit professionals with an orientation toward service, as if responsibility for patient care carried with it an obligation to abjure large financial rewards from scientific discovery. While, in truth, none could argue that the biomedical investigator had taken an oath of poverty, this ethic dictated that the fruits of research belonged to the ill rather than to the inventor. For example, the Harvard University medical faculty dedicated all patents to the public until 1975; thereafter, it adopted an aggressive patent policy. There is an obvious ambiguity between the dedication of inventions to the public and the entrepreneurial side of medicine.

Even though NIH had for almost two decades waived to medical schools the right to patents developed with federal funds, during the silicon-chip revolution, an inventor's share of royalties from federally supported research was severely restricted. Under the new patent law, this ceiling has been lifted and the inventor can gain handsomely if his patent proves to be commercially successful.

In addition, the salary structure in medical schools favored the faculty in the clinical sciences. With the changes in the patent law, the basic scientist now has a chance to gain substantial rewards from his research and to become the income peer of his clinical counterpart. A final distinction can be made between the silicon-chip revolution and that of recombinant DNA technology. The former technology obeys the strict laws of supply and demand while the latter has its biggest economic potential in the ever-increasing health service market.

A survey of historical spending patterns (Fig. 1) by industry and the NIH for health research and development (R&D) suggests the existence of three distinct phases occurring in the years 1947–1960, 1961–1979, and 1980–1982, respectively. During the first, industrial R&D dropped from 40 percent to 29 percent of the total, while the NIH share rose from 9 percent to 32 percent. Almost immediately after the war the NIH supported an ever-growing portion of health R&D activity while that fraction funded by industry kept falling, reaching a low of 25 percent in 1955. During the two decades after 1960, NIH and industry were in relative equilibrium, with the NIH funding about 38 percent of the total and industry about 25 percent. It is noteworthy that the dollar mixture of research, development, and application are very different in industry and NIH. For example, in 1980, basic research in the pharmaceutical industry accounted for only 10 percent of the R&D dollar and applied research for 44 percent of the total. In contrast, the NIH spent only about 12 percent of its budget on development but 52 percent on basic research.

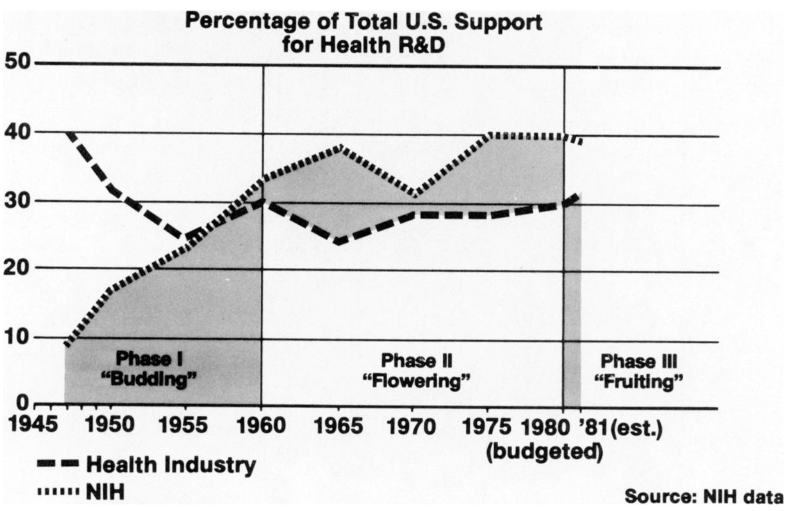

FIG. 1. Support for Health R&D: Relationship Between NIH and Health Industry Contributions.

After 1979, the federal percentage of total health research declined while that of industry increased sharply. Unfortunately, for 1980 and 1981, the years of greatest relevance to this comparison, we have only a budgeted total for the former year and estimates for the later, but several sources indicate that the changes are real.

Although the proportion of university research supported by industry seems to have remained nearly constant, the manner in which the funds are spent has changed sufficiently to attract national attention. In only a few years, almost a score of industries have entered into contracts with universities to support dedicated laboratories for work in medical sciences. Though we know relatively little about the details of these contracts—since information comes largely from media reports—what we do know indicates that the new industrial largess generally supports work related to the sponsors' products or to the markets they seek to enter. Universities receive funds for laboratory support and in exchange the industry obtains either a patent or an exclusive license to discoveries made in the laboratory it funds. It also gains unique access to an institutional knowledge base that may be at the frontier of science.

How should these shifts be interpreted? While there is no proven explanation, we can derive a plausible one from a study of industrial support for basic research (Fig. 2). As measured in constant 1972 dollars, basic research funded by all industry fell from $622 million in 1967 to $563 million in 1972 and then rose to $714 million in 1980 and $742 in 1981. Included in these figures is the industrial support for basic research (in 1972 dollars) to universities and colleges ($39 million in 1967, $53 million in 1972, and $70 million in 1980). Thus, until 1980 industry had kept its budget for basic research nearly constant. Instead, it invested dollars in applied and developmental activities.

Returning to biomedical R&D during phase II, industry appears to have made a conscious decision to depend upon university laboratories, supported largely by NIH, to conduct the basic biomedical research that leads to new knowledge. Indeed, estimates for fiscal year 1982 indicate that NIH supports 90 percent of all fundamental life science research in this country.

The revolutionary events coming in the decade of the 1970s, therefore, found industrial laboratories unprepared to exploit biomedical high technology and a staff trained for other scientific activities. By 1980, industry had already begun to seek a position in this field. The fastest way was to buy into existing programs. This decision to invest directly in ongoing or proposed university research offered a number of other advantages. Industry moved from a non-starter to a position near the finish line without incurring the major research costs of the technological breakthrough in biology. The federal budget had provided those dollars.

The health-related industries acquired a stake in high technology laboratories in areas of product interest, without having to make permanent commitments to staff benefits, long-term support, and retirement, which were university responsibilities. No industry could have hired such talent for in-house laboratories at so little cost. Although the dollars committed to these dedicated laboratories may appear large, they are spread out over a period of five to ten years and are small as compared with the federal investment in these program areas. If marketable technology emerges from these dedicated laboratories, the citizens of the nation will receive a double benefit—new health products will appear on the market, and taxes will return the NIH investment to the Treasury many times over. Time alone will tell whether the equation is favorable to the nation or to industry, or indeed to both.

It remains unclear whether the developments in Phase III are felicitous to the

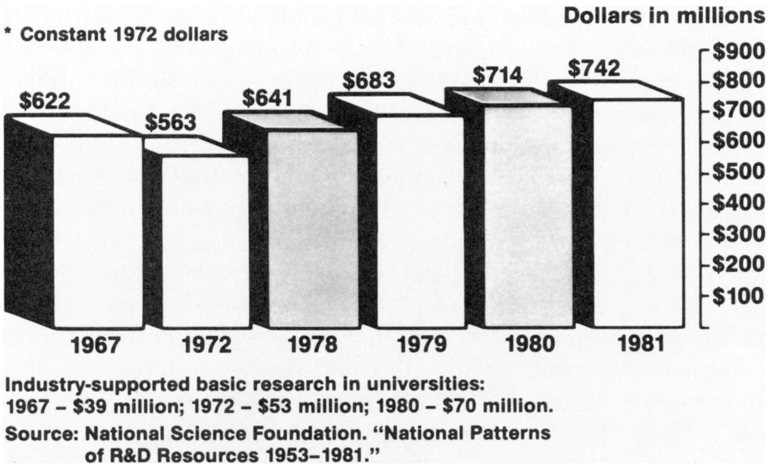

FIG. 2. Basic Research Funded by All American Industry.*

biomedical science base of the nation. There is no evidence that total investment in university-based bio-medical research (federal and industrial) is changing significantly, so one must assume that we are witnessing a displacement or substitution favoring a few select research centers. As industry-supported university laboratories increase in number there is a danger that program balance will shift to activities likely to provide short-term rewards. Industry must respond to stockholder pressure and seek near-term payoff on investments, whereas the federal government has no such responsibility. Industry will seek the best laboratories and the best scientists in the best schools. The rich will get richer and the poor get no assistance. This is a real cause for concern, since it exacerbates an existing imbalance. For example, the top twenty research centers in this country, 1 percent of the total number, received 44 percent of the NIH budget. To the other 1,180 institutions with NIH grants and contracts went the remaining 66 percent (Fig. 3).

And there is an additional danger that the goal of saleable products or processes will supplant the search for knowledge. At the same time some of the best scientists may be lured from the academic world and succumb to the inducements of profit-making organizations. Overriding these considerations is the need to maintain free and open discussion of scientific issues. Secrecy is antithetical to the vitality of science but may become a reality if industrial needs for exclusive licenses and patentable inventions become the goal of university laboratories. Secrecy in science presents a special concern to the NIH for its peer review system is built upon open and candid communication by its grantees. The responsibilities of these primary review groups cannot be met in an atmosphere of clandestine science, and a task already difficult and demanding, as budget realities reduce the relative dollar pool for support of science, will become impossible.

There is evidence from many sources that university administrators are concerned about this matter, as well as many others, for a number of major universities are actively discussing alternatives for maintaining the scholarly environment in the face of formidable social and economic pressure.

A final matter deserves attention. Can or will industry invest in university-based biomedical research at a level sufficient to compensate for the perceived short-fall in federal funding? While any answer must be a speculation, we can illuminate the matter by examining the size of the dollar commitment by the private sector resting in the balance. No scale exists to measure the appropriate budget for NIH. Funding levels are the result of a variety of scientific and political judgments that reach reconciliation in appropriations. One can, however, through indirection, obtain some first-order estimates. During the past several years NIH has judged that it would be desirable if competing grants in support of investigator-initiated research were fixed at 5,000 per year.

The NIH budget for FY 1983 will support only 4,100 such project grants, lacking $111 million to reach the desired number. Along with this, the budget request proposes to reduce payments to research sponsors for indirect costs by 10 percent, at a saving of $70 million. Finally the budget also presumes a reduction of 4 percent in support of non-competing continuation grant applications, giving a further reduction of about $61 million. The total for these sums, $241 million, does not take into account diminished activity in a variety of other research areas supported by NIH, costing about $250 million. Thus, conservative estimates of the short-fall for FY 1983 lie between a minimum of $241 million and an upper level of about half a billlion dollars.

This must be viewed against the private-sector allocation for health R&D which was $2.8 billion in 1981. The private sector would have to divert 8 percent of its 1981 R&D budget to university-based biomedical research to meet the lower level of short-fall and 17 percent if it deemed funding at the higher level to be desirable. The present commitment is at a level of about 3 percent.

In 1980, industry as a whole spent only 3 percent of its R&D budget on basic research and 78 percent on development. For the drug industry in 1980 the comparable figure for basic research was 9.6 percent of $1.5 billion, or $144 million. If industrial support for university-based biomedical research were to bridge the projected short-fall in the NIH budget and used funds only from its basic science budget, it must commit a sum almost twice the dollar amount that the drug industries budgeted for basic research in 1981.

We are witnessing a period of quantum changes in our knowledge of biology. At the same time, industry, universities, and government remain bound in a triple sym-

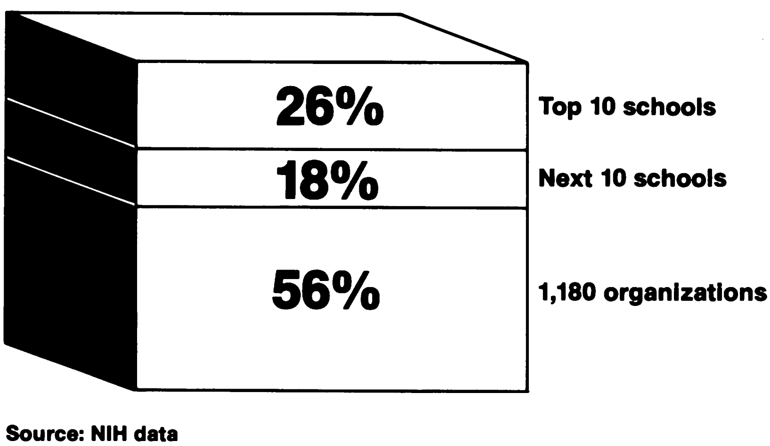

FIG. 3. Distribution of NIH Funding to Universities and Colleges (excluding construction) — 1981.

biotic relation. Historians may question whether each component has responded appropriately to a variety of societal and economic variables in an era of scientific transition. If the checks and balances of the triple helix behave like those in the helix of DNA, they will keep the component elements in the most productive relation.

It remains unclear what government can do to influence this process or even whether it should be more than an interested observer. It must at least monitor the changes, for the NIH has a huge investment in the science base of this country and a responsibility to maintain the vitality and productivity of biomedical research. It seems obvious that the private sector cannot commit sufficient funding to biomedical research in universities at a level that will have substantial impact on any but a selected few. Like the double helix of DNA, the triple helix of research, government, industry, and the university, is a fact of life. It is, however, a complex fact, dynamic and in evolution. Not enough time has passed to make a judgment on whether new support configurations will advance biomedical research, let alone sustain its present sound foundation.